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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/600,182

06/20/2003

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13681-012001

8996

26161 7590 04/30/2009
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EXAMINER

SAUCIER, SANDRA E

ART UNIT

PAPER NUMBER

1651

NOTIFICATION DATE

DELIVERY MODE

04/30/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No. 10/600,182	Applicant(s) BACH ET AL.	
	Examiner Sandra Saucier	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16-20,24-30 and 33-55 is/are pending in the application.
- 4a) Of the above claim(s) 16,17,54 and 55 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-20,24-30 and 33-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/11/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 16–20, 24–30, 33–55 are pending and claims 18–20, 24–30, 33–53 are considered on the merits. Applicant has elected the species of organ and CO.

Election/Restrictions

Newly submitted claims 54, 55 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: they are directed to treating disease states, while the original method claims are directed to treating donors/recipients or organs during transplantation procedures.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 54, 55 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections – 35 USC § 112

ENABLEMENT

Claims 18–20, 24–30, 33–53 remain/are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the transplantation of any organ with administration of CO and NO. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The invention, in one embodiment, is directed to the transplantation of organ(s), which is the elected species. This term is interpreted in the common scientific sense of a differentiated structure composed of tissues and cells.

The claims encompass the transplantation of any organ with the treatment of the recipient with administration of both CO and NO. The claims are interpreted in plain language which means that both CO and NO, which are

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gases are administered, not the administration of chemical compounds which release these gases in an indirect fashion nor transfer of genes which increase the concentration of these compounds *in vivo*.

The terms donor and recipient include humans as well as other animals.

There is no working example directed to transplantation of any organ. The working example is directed to a cell culture treatment of isolated hepatocytes or to protection against acute liver failure induced by TNF- α /D-gal. This is a model of fulminant hepatic failure (hepatitis). Even for this model, no concomitant administration of CO and NO is demonstrated. Rather it appears that CO administration is equivalent to NO administration. In any case, no art accepted transplantation model is presented which demonstrates superior survival of transplanted livers when CO with NO is administered to the recipient.

With regard to liver transplantation, no accepted animal model has been tested according to the specification for treatment with both CO and NO during the transplantation of liver. See Bishop *et al.* [V] where it is taught that liver has a better transplantation rate in rodents even when mismatched unlike other organs such as heart. Thus, liver is an organ which exhibits a less stringent matching requirement than other organs. Kanoria *et al.* [W] also discuss models for liver transplantation which include global ischemia. No art accepted animal model for liver transplantation has been used in an exemplification which clearly demonstrates efficacy of the treatment. Because liver may one of the most forgiving organs to transplant and no art accepted animal model for liver transplantation is presented, it is not reasonable to further predict that any and all patients receiving any organ can benefit from the treatment of the claimed method prior to, during or after transplantation.

Pharmaceutical therapies are unpredictable for the following reasons: (1) therapeutic compositions may be inactivated before producing an effect; (2) the therapeutic composition may not reach the target area; (3) other functional

properties, known or unknown, may make the therapeutic composition unsuitable for *in vivo* therapeutic use. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. App. & Inter. 1992).

Also, there is unpredictability in the art of administering CO in order to enhance the transplantation of organs such as liver, as evidenced by applicants' own published documents, see Calabrese *et al.* [C9] where CO administered to donor pigs prevents apoptotic events in the renal xenotransplantation model, but this treatment does not extend the survival of the graft, Cozzi *et al.* [C15]. Also, Soares *et al.*, 2009 still questions whether or not CO can be administered (to humans) therapeutically via inhalation, page 56, Box 1. Outstanding questions. Also, Meade *et al.* [AU] disclose that administration of NO to the human recipient of a lung transplant had no effect on the outcome of the transplantation procedure (abstract).

There is a body of literature which states that NO induces heme oxygenase-1, and that induction of heme oxygenase is the mechanism for the production of cellular CO, and that CO administration may have some benefits in some transplantation models, Otterbein *et al.* [C44], Hartsfield *et al.* [C23]. However, there is no evidence in the present application that NO and CO administration together produce results which are distinct from solely administering CO or NO alone to the recipient in an animal model of transplantation.

Although the specification discloses methods of administration of NO and CO *in vitro*, there are no data on the effectiveness of CO and NO both being administered to a transplant recipient and used in a therapeutic treatment of liver injury due to ischemia, reperfusion and immunogenicity which are some of the types of injury which occur during and after transplantation of a liver.

Therefore, in view of the nature of the invention, the state of the prior art, the amount of guidance present in the specification and the breadth of the claims, it would take undue experimentation to practice the claimed invention.

As set forth in *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA) 1970: [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of the enablement varies inversely with the degree of unpredictability of the factors involved. *Ex parte Humphreys*, 24 USPQ2d, 1260.

Applicant's arguments filed 2/11/09 have been fully considered but they are not persuasive.

Applicants argue that both NO and CO are suitable for therapeutic use and that the reasons in *Aggarwal* are not relevant to the administration of CO and NO. It may be that the applicant is correct in dismissing *Aggarwal* as relevant case law in this application, that is for others to decide; however, even if this were so, it does not overcome the enablement rejection, which is founded on the unpredictability in the art of transplantation medicine and the lack of evidence in the specification to enable such a method without undue experimentation and with a reasonable expectation of success.

The issue is: have applicants have provided evidence that their claimed method, which is the co-administration of CO and NO to the recipient of the transplant has a positive effect on the success of the transplantation which is more than the administration of CO or NO alone. This has not been demonstrated by applicants even for laboratory rodents.

Applicants argue that the references of Calabrese *et al.* and Cozzi *et al.* are not applicable because they are directed to administration of CO to the donor of the organ not the recipient, while this may be true, there still does not appear to be any literature directed to the co-administration of CO with NO to

the recipient of the organ transplant, which points up once again that this area is unexplored in the scientific literature.

Applicant presents a review that CO administration to rats and mice has a positive effect on transplantation results (Nakao *et al.* 2006). While this evidence is interesting, the claims are not limited to rats and mice administered CO alone. Experiments involving humans to date have not had the same success as with rats and mice and in fact, a review by Soares *et al.*, 2009 [U], still questions whether or not CO can be administered (to humans) therapeutically via inhalation. Since the specification discusses patients and humans, it is considered in light of the discussions in the specification and the lack of specificity in the claims, that donor and recipients of the treatment are within the scope of the claimed method and include human.

Applicants assert that there are many factors associated with the failure of the administration of NO by Meade *et al.*, such as improper timing of the NO administration, improper NO dosage, etc.. These are also parameters which influence the unpredictability in the practice of the invention over the scope of the claims. It also should be noted that Meade *et al.* is a human study and provides explicit evidence of unpredictability in the art. Thus, NO administration alone has not been demonstrated to have a predictable favorable outcome in a transplantation procedure.

Applicants argue that the results presented using models of inflammation in mice that there is a synergism between CO and NO in providing cytoprotection, which they are the first to show. Applicants, therefore, appear to admit that they are in the early states of development in a technology which the cited art shows is unpredictable.

A synergistic effect is not required to be present in the claim language. However, if the combined treatment of NO and CO to the recipient has no increased effect over the effect obtained with NO or CO administer individually, there are enablement issues present with the claimed method because the

claimed method cannot be practiced with a reasonable expectation of success over the scope of the claim, i.e. with humans. Success in organ transplantation being for example, a decrease organ rejection rate, a decrease in complications, a shortened recovery time, etc..

Applicants claim the co-administration of CO and NO to the recipient of the transplant. Thus, at least a positive effect of the use of NO and an additive positive effect, if not synergistic effect should be demonstrated when CO is added as an adjunct, in at least an accepted animal model.

"Where the claimed invention is the application of an unpredictable technology in the early states of development, an enabling description in the specification must provide those skilled in the art with a specific and **useful** teaching." *Genentec, Inc. v. Novo Nordisk, A/S*, 42 USPQ 2d 1001 (Fed. Cir. 1997).

Presentation of appropriate objective evidence might promote prosecution.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The

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fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
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